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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,346	01/02/2004	Ron S. Israeli	41426-FA-PCT-US/JPW/CY	7618

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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
05/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/751,346	ISRAELI ET AL.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,23-25 and 27-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,23-25,27-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/5/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Arguments and Amendements

The remark filed on 2/5/2007 in response to the previous Non-Final Office Action (8/2/06) is acknowledged and has been entered.

Claims 1-20, 22, 26 and 22-58 have been cancelled. Claims 21, 23-25, 27-31 are pending and under consideration.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 2/5/07 are/is considered by the examiner and initialed copies of the PTO-1449 are enclosed.

Rejections and/ Objections Withdrawn

1. Rejection of claims 21, 23-25, 30-31 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the claimed invention is withdrawn in view of applicant's argument.

2. It is acknowledged that applicant submits exhibit A, a supplement applicant data sheet, and amendment to specification to remove the claim to benefit of US serial No 08/325553 filed 10/18/1994 and 07/973337, filed 11/5/1992. Thus, no new declaration is further required.

Response to Arguments

Priority

The Office has established effective filing date 1/2/2004 for instant claims and reason as stated again below.

> Acknowledgement is made of applicant's claims to an earlier effective filing date PCT/US96/024224 filed on 2/23/1996. Claims 21, 23-25, 27-31, as filed on 1/2/04 and amended on 5/12/06, are drawn to a method of ablating, killing, or eliminating a normal or prostate cancer cells comprising binding an antibody to outer membrane domain of PSMA or antibody bound to a substance effective to kill the cells. Upon review of specification of the applications, it is noted that the PCT/US96/024224 as filed although state, on paragraph 165, "*therapeutic agent comprising antibodies or ligand(s) directed against PSM antigen and a cytotoxic agent conjugated thereto or antibodies linked enzymes which activate prodrug to kill the tumor, the cytotoxic agent may either be a radioisotope or toxin*" does not provide adequate **support** for the method of ablating, killing, or eliminating a normal or prostate cancer cells comprising binding an antibody to outer membrane domain of PSMA. Therefore, the claims 21, 23-25, 27-31, will have current filing date 1/2/2004.

The response filed 2/5/2007 has been carefully considered but is deemed not to be persuasive. The response states that *applicants note that support for the method of base claim 21 can be found in the specification as originally filed and in PCT/US9602424, for example, at page 32, line 23 and page 33, line 2, which discloses selecting hydrophilic amino acid sequence to generate antibodies and recite that with the protein sequence information, antigenic areas may identified and antibodies directed against these areas may be generated and targeted to the prostate cancer for imaging the cancer or therapies.* In response to this argument, description of protein having antigenic activity and simply statement of using the antibody targeting the cancer is different from claiming a method of ablating, killing or eliminating normal, benign hyperplastic and cancerous prostate epithelial cells.... Generally stating cancer therapy does not encompass the claimed method steps of ablating, killing, or eliminating the normal, benign hyperplastic, and cancerous prostate epithelial cells by binding the antibody to outer membrane domain of PMSA. Therefore, Applicant's argument has not been found persuasive, effective filing date for the claims is 1/2/2004 as stated in the previous office action.

Rejection under 35 USC § 112, second paragraph

Claims 21, 23-25, 27-31 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as stated again below.

> **The following is a quotation of the second paragraph of 35 U.S.C. 112:**
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
>
> Claims 21, 23-25, 27-31 are vague and indefinite because it is not clear how the cells are killed, ablated or eliminated by an antibody in the amended claim 21. The original claims comprising a biological agent is broadly interpreted as an agent comprising binding portion and killing portion. However, instant claims are amended by replacing biological agent with an antibody. Thus, it is not clear how the antibody alone bind to surface of the cells and kill cells or under condition effective to kill cells. It is also not clear how antibody is bound to a substance effective to kill, ablate or eliminate cells in claim 27. It is not clear that the substance is conjugated to antibody or not. Claims also render the dependent claims indefinite.

The response filed 2/5/2007 has been carefully considered but is deemed not to be persuasive. The response states that *antibody-dependent cell-mediated cytotoxicity (ADCC) is*

one art-recognized mechanism and also submits two abstracts to support the argument. Applicant further argue that conjugation to an antibody is one means by which a substance effective to kill, ablated or eliminated prostate cell can be bound to he outer membrane domain of prostate specific membrane antigen on cells. In response to this argument, first, the rejection under the second paragraph of 35 U.S.C. 112 is based on whether the claimed invention is clearly stated in the claim. The Office agrees that ADCC is known mechanism in the art, which involves activation of NK cells recognizing and killing antibody-coated target cells being infected or tumor cells specifically expressing the antigen bound by antibody. If applicant consider that such mechanism involved in the claimed invention. It is Not clear why normal cell are also eliminated. One skilled in the art has recognized that PSMA is a prognostic proliferation marker and is expressed primarily in benign and cancerous prostate epithelia cells. (Elgamal et al., Semin surg Oncol, vol 18 10-6, 2000, abstract). It is not clear that if normal prostate cell does not express such antigen, how can it be eliminated or killed. The specification does not provide any teaching on that the killing of PSMA expressing cells are through the mechanism of ADCC or any antibody to PSMA disclosed in the specification having such ability when binding to the PSMA expressing cells.

In addition, in the rejection, the office states "it is also not clear how antibody is bound to a substance effective to kill, ablate or eliminate cells in claim 27. It is not clear that the substance is conjugated to antibody or not". Term "bound" is clear, but "substance effective to kill....is not clear. It is not clear that the term "substance" means antigen expressed in cells or the cytotoxic agent conjugated to the antibody. Thus, Applicant's argument has not been found persuasive, and clarification and amendments are required.

Rejection under 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. ***New matter***

Claims 21 and 23-25 remain rejected under 35 U.S.C, 112, first paragraph as new matter stated below since applicant does not response and comment on the rejection.

> It is noted that the claims 21, 23-25 as newly amended claims recite " eliminating ...epithelial cells comprising an antibody which binds to an outer membrane domain of prostate specific membrane antigen and contacting said cell with antibody under conditions effective to permit both binding of the antibody to the outer membrane domain of the prostate specific membrane antigen and .... eliminating said cells", which is not supported by instant specification. Instant specification as filed, although provide teaches that antibodies against PSM coupled with a cytotoxic agent will be useful to eliminate prostate cancer cells (page 68, line 16-24) does not provide sufficient support for the instant claims reciting eliminating prostate cancer cell or epithelial cells by an antibody only.

The response filed 2/5/2007 has been carefully considered but is deemed not to be persuasive. The response states that the specification recited that with the protein sequence information, antigenic areas may be identified and antibodies directed against these areas may be generated and targeted to the prostate cancer for imaging the cancer of therapies. In response this argument, applicant claims a specific prostate cancer therapy by antibody mediated eliminating the cells. The specification neither provides an antibody having such function, nor a method of eliminating a normal, BPH, or prostate cancer epithelial cells by an antibody binding to outer membrane of prostate cancer cells.

2. ***Written description***

Claims 21, 23-25, 27-31 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> The claims encompass a method of killing, ablating, or eliminating prostate cells comprising an antibody binding to outer member domain of PSMA and under condition effective to permit both binding of the antibody to the outer membrane domain of the prostate specific membrane antigen and ablating, killing, or eliminating the cells, wherein the antibody also is bound to substance comprising a toxin effective to kill or eliminate said cells.

The specification on paragraph 244-245, teaches a computer predicted specific membrane-spanning domain of PSMA and states this data enables prediction of inner and outer membrane domains of the PSM antigen which aids in designing antibodies for uses in targeting and imaging prostate cancer. However, the specification neither discloses any of such antibodies which specifically bind to outer membrane domain of the this protein nor any method using such antibody or any antibody bound to a toxin binding to the surface of the prostate cells and kill, or eliminates the cell due to the binding of antibody to outer membrane domain.

While the specification discloses a starting point for making antibodies that may bind to the outer membrane of PSMA protein on the prostate cell, the disclosure does not set forth sufficient procedures that will necessarily lead to kill, ablate, or eliminate the prostate cell with such antibody or antibody bound to a substance. The application does no more than describe the desired function of the claimed antibodies encompassed by the claimed invention and does not contain sufficient information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention.

The claimed methods depend upon computer predicted protein sequence of PSMA to design antibodies that specifically bind to the outer membrane of the protein on the prostate cancer cells and using this antibody to binding to surface of the cell and further kill or eliminate the cells. Without such antibodies, which have been tested for certain of binding, the skilled artisan can not practice the claimed method for killing or eliminating the prostate cells. It means little to invent a method if one does not have possession of the antibodies that is (are) essential to practice the method. Without possession of the antibodies, the claimed endpoints are illusory and there is no meaningful possession of the method.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. The claimed methods depend upon computer predicted protein sequence of PSMA to design antibodies that specifically bind to the outer membrane of the protein on the prostate cancer cells and using this antibody to binding to surface of the cell and further kill or eliminate the cells. Without such antibodies, which have been tested for certain of binding, the skilled artisan cannot practice the claimed method of treatment. It means little to invent a method if one does not have possession of the antibodies that is (are) essential to practice the method. Without possession of the antibodies, the claimed endpoints are illusory and there is no meaningful possession of the method.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

Applicant has been directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Also, see MPEP 2163.

The response filed 2/5/2007 has been carefully considered but is deemed not to be persuasive. The response states that *the specification has disclosed selecting hydrophilic amino acid to generate antibodies and antigenic areas may be identified and antibodies directed against these areas may be generated ant targeted to the prostate cancer for imaging or therapies.* In response to this argument, the claimed invention is drawn to a method of ablating, killing or eliminating normal, benign, hyperplastic, and cancerous prostate epithelial cells with antibody specifically to outer membrane domain of PSMA. As stated in the previous office action, it means

little to invent a method if one does not have possession of the antibodies that is (are) essential to practice the method. Without possession of the antibodies (that specific to the outer membrane domain), the claimed endpoints are illusory and there is no meaningful possession of the method. Generally stating "antibodies against these areas may be generated and targeted for cancer therapy" does not support the claimed invention drawn to a method of ablating, killing, or eliminating the normal, BHP, or cancer prostate epithelial cell. In addition, the specification neither describe the claimed method step of ablating, killing, or eliminating the prostate epithelial cells, nor provide information how the method is performed by binding an antibody to the outer membrane domain of the PMSA. Therefore, one of skill in the art would reasonably conclude that the inventor(s), at the time the application was filed, **did not have** possession of the claimed method. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained.

Rejection under 35 USC § 103

Claims 21 and 23-25, 30-31 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al., (prostate vol 28, page 266-271, 1996) in view of Horoszewicz et al., (US Patent, 5162504, Nov, 1992) and/or Horoszewicz et al., (Anticancer Res, vol 7, page 927-35, 1987).

> The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
>
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
>
> 1. Determining the scope and contents of the prior art.
> 2. Ascertaining the differences between the prior art and the claims at issue.
> 3. Resolving the level of ordinary skill in the pertinent art.
> 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Murphy et al., teach antibody 3F5.4G6, which reacts with the extracellular domain (outer membrane) of PSMA (abstract).

Murphy do not teach a method of ablating, killing, or eliminating the prostate cancer cells by antibody or antibody conjugate to a toxin.

Horoszewicz et al., disclose a method of treating prostate cancer with prostate antigen specific antibody conjugated with a toxin (column 7, line 25-30). Horoszewicz et al., also disclose that the antibody to prostate antigen with a pharmaceutical carrier is used to treat human prostate carcinoma patient in conjunction with a toxin either non-covalent or covalent linkages (column 11-12). Horoszewicz et al., further disclose that conjugated antibodies can be administered to patients to achieve enhance tumoricidal effects through the cytotoxic action (column 13, line 7-13). Horoszewicz et al., disclose antibody 9H10-A4H, which only recognizes the surface of prostate cancer cells, LNCap (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method to kill, ablate, or eliminate the prostate cells comprising providing antibody binding to an outer membrane domain of prostate specific membrane antigen and toxin to eliminate or kill the cells. One of ordinary skill in the art would have been motivated with a reasonable expectation of success to apply the antibodies taught by Murphy et al., to Horoszewicz's method to enhance the prostate cancer treatment by selectively binding the antibody-conjugate to the surface of the membrane of the prostate cancer cells. Because Murphy et al., have shown the antibodies specifically bind to the extracellular domain (outer membrane domain) of prostate specific membrane antigen and Horoszewicz et al., have taught the method of treating prostate cancer cells by antibody-toxin conjugate, one of ordinary skill in the art would have been motivated with a reasonable expectation of success to kill or eliminate the cancer cells with the method.

The response filed 2/5/2007 has been carefully considered but is deemed not to be persuasive. The response states that Murphy et al., is published in April 1996 after Feb 24, 1995 effective filing date of the subject application and filing date of PCT/US96/02424, Feb 23, 1996. In response to this argument, instant claims are not supported by the priority documents as discussed above (priority). Thus, Murphy et al., is prior art. Murphy et al., in combination with the Horoszewicz et al., is obvious over the claimed invention. Thus, Applicant's argument has not been found persuasive, and the rejection is maintained.

Conclusion

NO claim is allowed.

Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao,
Examiner
Art Unit 1642

LY

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